Effective Health Care

Failure to Thrive

Results of Topic Selection Process & Next Steps

The nominator, the American Academy of Pediatrics (AAP), is interested in an AHRQ evidence review on defining failure to thrive (FTT), mapping the natural history and progression of FTT, and managing treatment for FTT in infants and toddlers. This includes benefits and harms of diagnostic testing for the underlying cause(s) of FTT and determining when hospitalization is the appropriate next step. It is the hopes of the AAP to use an AHRQ evidence review to publish a clinical practice guideline on the management of FTT, and to use the gaps in evidence to identify priorities for future research. Due to limited program resources, the Effective Health Care (EHC) program will not develop a review at this time. No further activity on this topic will be undertaken by the EHC Program.

Topic Brief

Topic Name: Failure to Thrive

Topic #: 0726

Nomination Date: November 2, 2016

Topic Brief Date: February 2017

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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Summary of Key Findings

- Appropriateness and importance: The nomination is both appropriate and important.
- Duplication: A new evidence review examining failure to thrive would not be duplicative. We found only one systematic review published in the last five years. This 2014 Cochrane review examines zinc supplementation in children between six months and twelve years with growth failure. Also, of note, AHRQ published a systematic review on Failure to Thrive in 2003.
- Impact: A new evidence review on the topic would have high impact. The standard of care is unclear. In 2016, American Family Physician published a clinical practice guide for managing FTT. While these are not official guidelines, they include clinical practice recommendations (with strength of evidence), and cover most of the scope of the nomination. The recommendations were based on "consensus, disease-oriented evidence, usual practice, expert opinion, or case series," evidence, suggesting a

knowledge gap. There is also practice variation. Because there are no official guidelines in existence, physicians manage and treat FTT in a variety of ways.

- Feasibility: An AHRQ evidence review is feasible at this time.
  - *Size/scope of review:* Our search of PubMed for failure to thrive resulted in 367 unique titles. Upon title and abstract review of all 367 results, we identified a total of 37 studies potentially relevant to the key questions in the nomination. Six published studies were identified for KQ 1 (definition of FTT), 14 studies that examine the natural history and risk factors (KQ 2) for FTT were identified, 13 studies cover KQ 3 (regarding diagnostic testing for the underlying cause of FTT), 13 published studies examine various feeding interventions and therapies for FTT (KQ 4a-f), and five studies look into hospitalization in patients with FTT (KQ 5 and 5a). While studies were found for all key questions, no RCTs were identified in our search results.
  - *Clinicaltrials.gov:* We identified seven clinical trials. All seven examine interventions for treating FTT.
- Value: The nomination has high value potential. The American Academy of Pediatrics will create a clinical practice guideline based on the findings of a systematic review. Currently, no official, evidence review-based guidelines exist. The information provided in an AHRQ product will also help the AAP identify future research priorities, which is one of the AAP's goals of an evidence review.

Table of Contents

Introduction ..... 1 "
Methods ..... 4 "
Appropriateness and Importance ..... 4 "
Desirability of New Review/Duplication ..... 4 "
Impact of a New Evidence Review ..... 4 "
Feasibility of a New Evidence Review ..... 4 "
Compilation of Findings ..... 4 "
Results ..... 4 "
Appropriateness and Importance ..... 5 "
Desirability of New Review/Duplication ..... 5 "
Impact of a New Evidence Review ..... 5 "
Feasibility of a New Evidence Review ..... 5 "
Value ..... 7 "
Summary of Findings ..... 7 "
References ..... 8 "
Appendices ..... 11 "
Appendix A. Selection Criteria Summary ..... A-1 "
Appendix B. Search Strategy & Results (Feasibility) ..... B-1 "

Introduction

Failure to thrive (FTT) is a clinical finding, often the result of an underlying medical condition, malnutrition, or neglect. It is used to describe children whose weight is in the second or lower percentile, or whose weight gain has plateaued.[1] There is no standard definition for FTT, and its natural progression, including long term effects, is not well researched. There is some debate in the medical community about the most effective therapy to ameliorate FTT, given that every case is different. Treatments can range from parent education, all the way to hospitalization and insertion of a feeding tube. Understanding the best treatments for failure to thrive begins, first, with defining it and mapping its natural history.

Topic nomination #0726 was received on November 2, 2016. It was nominated by the American Academy of Pediatrics (AAP). This nomination was submitted by the American Academy of Pediatrics. After some discussion, the key questions and PICOs (population, interventions, comparators, and outcomes) were updated to widen the age of interest from, initially, 2 months to three years, to birth to three years. Extremely-low-birth-weight infants were explicitly excluded, upon request of the nominator. The key questions for this nomination are:

Key Question 1. What is the best way to define FTT?

Key Question 2. What is the natural history of failure to thrive with regard to growth, intellectual development, and other outcomes? What are risk factors for worse outcomes?

Key Question 3. What are the benefits and harms of diagnostic tests to identify the underlying cause in infants identified as having failure to thrive?

Key Question 4. What are the benefits and harms of the following therapies for failure to thrive?

a. Behavioral feeding interventions
b. Oral supplement feeding
c. Enteral tube feeding
d. Parental education
e. Increased caloric density of feeds
f. Other intervention

Key Question 5. What are the benefits and harms of hospitalization for evaluation and treatment of failure to thrive?

a. Which patients are most likely to benefit from hospitalization?

To define the inclusion criteria for the key questions we specify the population, interventions, comparators, and outcomes of interest. See Table 1.

Table 1. Key Question and PICOs "

Key Questions	1. What is the best way to define FTT?	2. What is the natural history of failure to thrive with regard to growth, intellectual development, and other outcomes? What are risk factors for worse outcomes?	3. What are the benefits and harms of diagnostic tests to identify the underlying cause in infants identified as having failure to thrive?	4. What are the benefits and harms of the following therapies for failure to thrive? a. Behavioral feeding interventions b. Oral supplement feeding c. Enteral tube feeding d. Parental education e. Increased caloric density of feeds f. Other intervention	5. What are the benefits and harms of hospitalization for evaluation and treatment of failure to thrive? a. Which patients are most likely to benefit from hospitalization?
Population	Babies and children up to three years old, without previously recognized underlying cause for poor growth	Babies and children up to three years old, without previously recognized underlying cause for poor growth	Babies and children up to three years old, without previously recognized underlying cause for poor growth, identified as having FTT	Babies and children up to three years old, with or without previously recognized underlying cause for poor growth, identified as having FTT	Babies and children up to three years old, with or without previously recognized underlying cause for poor growth, identified as having FTT
Interventions	NA	NA	Diagnostic tests may include but are not limited to: complete dietary history and psychosocial evaluation, CBC, basic metabolic profile, lead screening, stool pathogens, stool fat, cystic fibrosis screening, TSH, CBC/ESR, urinalysis, liver function tests, cardiac ultrasound + ECG	Behavioral feeding interventions, oral supplement feeding, enteral tube feeding, parental education (pamphlet, feeding class, one-on-one coaching with doctor or nurse, feed monitoring, etc.), increasing caloric density of feeds, other interventions	Hospitalization
Comparators	NA	NA	No diagnostic screening, usual care	Expectant management, active therapy	Outpatient management or evaluation, other case management or evaluation
Outcomes	1. Diagnostic—identifying those with underlying disease or cause 2. Therapeutic—identifying those who can benefit from	Growth (height, weight, and head circumference); intellectual development; diagnosis of underlying pathology causing failure	Identification and intervention in abuse and neglect associated with failure to thrive; discomfort, adverse events, and over-	Growth (height, weight, and head circumference); intellectual development; diagnosis of underlying pathology causing failure	Growth (height, weight, and head circumference); intellectual development; diagnosis of underlying pathology causing failure

	therapy 3. Reduction in morbidity and mortality, reduction of long term consequences of failure to thrive.	to thrive; identification and intervention in abuse and neglect associated with FTT	diagnosis of underlying pathology from diagnostic testing; stress for child and caregivers; inappropriate disruption of family; harm to family-physician relationship; financial burden	to thrive; identification and intervention in abuse and neglect associated with FTT; improvement in behavior and psychosocial problems; discomfort and adverse events with supplemental feeding; stress for child and caregiver; inappropriate disruption of family; harm to family-physician relationship; financial burden	to thrive; identification and intervention in abuse and neglect associated with FTT; improvement in behavior and psychosocial problems; discomfort and adverse events with supplemental feeding; stress for child and caregiver; inappropriate disruption of family; harm to family-physician relationship; financial burden

Abbreviations: CBC=Complete Blood Count; ECG=Echocardiogram; ESR=Erythrocyte Sedimentation; FTT=Failure to Thrive; TSH=Thyroid Stimulating Hormone

Methods

To assess topic nomination *#0726 Failure to Thrive* for priority for a systematic review or other AHRQ EHC report, we used a modified process based on established criteria. Our assessment is hierarchical in nature, with the findings of each step in our assessment determining the need for further evaluation of the next step. Details related to our assessment are provided in Appendix A.

1. " Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. " Establish the overall *importance* of a potential topic as representing a health or " healthcare issue in the United States. "
3. " Determine the *desirability of new evidence review* by examining whether a new " systematic review or other AHRQ product would be duplicative. "
4. " Assess the *potential impact* a new systematic review or other AHRQ product.
5. " Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. " Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance (see Appendix A).

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews pertaining to the key questions of the nomination. Table 2 includes the citations for the reviews that were determined to address the key questions.

Impact of a New Evidence Review

The impact of a new evidence review was assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether a new review could influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of a New Evidence Review

We conducted a literature search in PubMed from December 2011 to December 2016 (Appendix B). Because a small number of articles were identified, we reviewed all of the titles and abstracts for inclusion and classified identified studies by study design, to assess the size and scope of a potential evidence review. See *Table 2, Feasibility Column, Size/Scope of Review Section* for the citations of included studies.

Value

We assessed the nomination for value (see Appendix A). We considered whether a partner organization could use the information from the proposed evidence review to facilitate evidence-based change; or the presence of clinical, consumer, or policymaking context that is amenable to evidence-based change.

Compilation of Findings

We constructed a table outlining the selection criteria as they pertain to this nomination (see Appendix A).

Results

Appropriateness and Importance

This is an appropriate and important topic. According to UpToDate, around 3-10% of children in primary care are found to have FTT.[1] There is no single, standardized definition of FTT, and because of this, the point at which to treat, and what treatment to use is contested.

Desirability of New Review/Duplication

A new evidence review examining failure to thrive would not be duplicative. We found only one Cochrane review in the last five years, examining zinc supplementation for preventing mortality, morbidity, and growth failure in children aged six months to 12 years of age.[2] This covers a small portion of the proposed review's scope.

Impact of a New Evidence Review

The impact of a new review would be high. The standard of care is not clear. In 2016, American Family Physician published a clinical practice guide for managing FTT. While these are not official guidelines, they include clinical practice recommendations (with strength of evidence), and cover most of the scope of the nomination.[3] This practical guide includes etiology, prevention, diagnostic evaluation, and treatment, but is not based on a systematic review. The guide also includes clinical recommendations for physical measurements, which measurement charts a physician should use based on patient age, and recommendations about routine lab testing and hospitalization. These recommendations were rated using the SORT rating system, and all recommendations were graded a "C," meaning the recommendation is based off of "consensus, disease-oriented evidence, usual practice, expert opinion, or case series," evidence, suggesting a knowledge gap. Additionally, there is uncertainty about the utility of a family physician-based practical guide by a pediatric specialty group. There is also practice variation. Because there are no official guidelines in existence, physicians manage and treat FTT in a variety of ways.

Feasibility of a New Evidence Review

A new evidence review on failure to thrive is feasible. We identified a total of 37 studies pertaining to the key questions. Six studies on the definition of failure to thrive (KQ 1),[4-9] 14 studies examining the natural history and risk factors of FTT (KQ 2),[4,6-18] 12 studies that research diagnostic tests to identify the underlying cause of FTT (KQ 3),[14,16,19-28] 13 studies that examine the various interventions to treat FTT (KQ 4a-4f),[7,10,16,29-38] and five studies on treating FTT with hospitalization (KQ 5-5a).[7,29,30,39,40] The number of studies identified across interventions for treating FTT (KQ 4) is small—only 13 studies across six interventions. No RCTs were identified among the 37 total studies.

We identified seven clinical trials.[41-47] All seven examine interventions for treating FTT, and five have been recently completed.

Table 2. Key question with the identified corresponding evidence reviews and original research

Key Question	Duplication (Completed or In-Process Evidence Reviews)	Feasibility (Published and Ongoing Original Research)
1: Definition	None identified	<u>Size/scope of review</u> Relevant Studies: 6 • Longitudinal: 1[4] • Cross-Sectional Observational: 1[5] • Observational: 1[6] • Retrospective Chart Review: 3[7-9] <u>ClinicalTrials.Gov</u> Relevant studies: 0
2: Natural history and risk factors	None identified	<u>Size/scope of review</u> Relevant Studies: 14 • Observational: 2[6,10]

Key Question	Duplication (Completed or In-Process Evidence Reviews)	Feasibility (Published and Ongoing Original Research)
		• Longitudinal: 4[4,11-13] • Prospective Cohort: 1[14] • Cross-Sectional: 1[15] • Retrospective Chart Review: 5[7-9,16,17] • Econometric Analysis: 1[18] ClinicalTrials.Gov Relevant studies: 0
3: Diagnostic tests for underlying cause of FTT	None identified	Size/scope of review Relevant Studies: 12 • Prospective Case Control: 1[19] • Prospective Cohort: 2[14,20] • Observational: 1[21] • Retrospective Cohort: 2[22,23] • Retrospective Observational: 2[24,25] • Retrospective Chart Review: 4[16,26-28] ClinicalTrials.Gov Relevant studies: 0
4a: Behavioral feeding interventions	None identified	Size/scope of review Relevant Studies: 1 • Observational: 1[10] ClinicalTrials.Gov Relevant studies: 0
4b: Oral supplement feeding	Total number of completed or in-process evidence reviews: 1 • Cochrane: 1[2]	Size/scope of review Relevant Studies: 6 • Cohort: 2[29,30] • Case Series:1[31] • Retrospective Chart Review: 3[7,32,33] ClinicalTrials.Gov Relevant studies: 4 • Complete: 4[41-44]
4c: Enteral tube feeding	None identified	Size/scope of review Relevant Studies: 3 • Observational: 1[34] • Retrospective: 1[35] • Retrospective Chart Review: 1[7] ClinicalTrials.Gov Relevant studies: 2 • Complete: 2[41,45]
4d: Parental education	None identified	Size/scope of review Relevant Studies: 3 • Observational: 2[10,36] • Retrospective Chart Review: 1[16] ClinicalTrials.Gov Relevant studies: 0
4e: Increased caloric density of feeds	None identified	Size/scope of review Relevant Studies: 1 • Retrospective Chart Review: 1[16] ClinicalTrials.Gov Relevant studies: 0

Key Question	Duplication (Completed or In-Process Evidence Reviews)	Feasibility (Published and Ongoing Original Research)
4f: Other therapeutic interventions	None identified.	Size/scope of review Relevant Studies: 2 • Validity: 1[37] • Retrospective Chart Review: 1[38] ClinicalTrials.Gov Relevant studies: 2 • Recruiting: 1[46] • Active, not recruiting: 1[47]
5: Benefits and harms of hospitalization	None identified	Size/scope of review Relevant Studies: 5 • Cohort: 2[29,30] • Retrospective: 1[39] • Retrospective Chart Review: 2[7,40] ClinicalTrials.Gov Relevant studies: 0
5a: Who would more likely benefit from hospitalization	None identified	Size/scope of review Relevant Studies: 2 • Cohort: 2[29,30] ClinicalTrials.Gov Relevant studies: 0

Abbreviations: FTT=Failure to Thrive

Value

The nomination has high value potential. The American Academy of Pediatrics (AAP) will create a clinical practice guideline based on the findings of a systematic review. Currently, no official, evidence review-based guidelines exist. The information provided in an AHRQ product will also help the AAP identify future research priorities, which is one of the AAP's goals of an evidence review.

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Appendices

Appendix A: Selection Criteria Summary !

Appendix B: Search Strategy & Results (Feasibility) !

Appendix A. Selection Criteria Summary (

Selection Criteria	Supporting Data
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes, this topic represents interventions available in the US.
1b. Is the nomination a request for a systematic review?	Yes, this topic is a request for a systematic review on FTT.
1c. Is the focus on effectiveness or comparative effectiveness?	The focus of this review is on effectiveness.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes, it is biologically plausible. Yes, it is consistent with what is known about the topic.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Yes, this topic represents a significant burden. According to UpToDate, around 3-10% of children in primary care are found to have FTT.[1]
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes, this topic affects heath care decisions for a large, vulnerable, pediatric population. Severe FTT may require hospitalization.
2c. Represents important uncertainty for decision makers	Yes, this topic represents important uncertainty for decision makers. There is no single, standardized definition of FTT, and because of this, the point at which to treat, and what treatment to use is contested.
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes, this nomination addresses both benefits and potential harms of diagnostic tests for identifying the underlying cause of FTT, the therapies to treat FTT, and hospitalization for FTT.
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes, this nomination represents a condition that may results in high costs due for consumers and payers.
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	A new evidence review examining failure to thrive would not be duplicative. We found one systematic review in the last five years. This 2014 Cochrane review examines zinc supplementation in children between six months and twelve years with growth failure.[2]
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	The standard of care is unclear. In 2016, American Family Physician published a clinical practice guide for managing FTT. While these are not official guidelines, they include clinical practice recommendations (with strength of evidence), and cover most of the scope of the nomination.[3] The recommendations were based on “consensus, disease-oriented evidence, usual practice, expert opinion, or case series,” evidence, suggesting a knowledge gap.

4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes, there is practice variation. Because there are no official guidelines in existence, physicians manage and treat FTT in a variety of ways.
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	Size/scope of review: Our search of PubMed for failure to thrive resulted in 367 unique titles. Upon title and abstract review of all 367 results, we identified a total of 37 studies potentially relevant to the key questions in the nomination. While studies were found for all key questions, no RCTs were identified in our search results. Detailed Feasibility: Six published studies were identified for KQ 1 (definition of FTT),[4-9] 14 studies that examine the natural history and risk factors (KQ 2) for FTT were identified,[4,6-18] 12 studies cover KQ 3 (regarding diagnostic testing for the underlying cause of FTT),[14,16,19-28] 13 published studies examine various feeding interventions and therapies for FTT (KQ 4a-f),[7,10,16,29-38] and five studies look into hospitalization in patients with FTT (KQ 5 and 5a).[7,29,30,39,40] Clinicaltrials.gov: We identified 7 clinical trials.[41-47] All seven examine interventions for treating FTT, and five have been recently completed.
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change	Yes, this nomination exists within a favorable clinical, consumer, and policy-making context. A review on this topic would inform the creation of AAP clinical practice guideline as well as impact clinical decision-making to optimize benefits of treatment while reducing potential harms. Parents and doctors will be able to use the results of an AHRQ systematic review to aid in FTT treatment decision-making.
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	Yes, the AAP has partnered and will create an evidence-based guideline based on the results of an AHRQ evidence review.

Abbreviations: AAP=American Academy of Pediatrics; AHRQ=Agency for Healthcare Research and Quality; FTT=Failure to Thrive

Appendix B. Search Strategy & Results (Feasibility) (

Topic: Failure to thrive Date: December 12, 2016 Database Searched: MEDLINE (PubMed)	
Concept	Search String
Failure to Thrive	((("Failure to Thrive"[Mesh]) OR (("failure to thrive"[Title] OR "substandard growth"[Title] OR "faltering weight"[Title] OR "weight faltering"[Title]))))) OR "growth failure"[Title]
NOT	
Not Editorials, etc.	((((((("Letter"[Publication Type]) OR "News"[Publication Type]) OR "Patient Education Handout"[Publication Type]) OR "Comment"[Publication Type]) OR "Editorial"[Publication Type])) OR "Newspaper Article"[Publication Type]
Limit to last 5 years ; human ; English ;	Filters activated: published in the last 5 years, Humans, English.
N=295	
Systematic Review N=5	PubMed subsection “Systematic [sb]”
Randomized Controlled Trials N=61	Cochrane Sensitive Search Strategy for RCT’s “(((((((((groups[tiab])) OR (trial[tiab])) OR (randomly[tiab])) OR (drug therapy[sh])) OR (placebo[tiab])) OR (randomized[tiab])) OR (controlled clinical trial[pt])) OR (randomized controlled trial[pt])”
Other N=229	

Clinicaltrials.gov

15 studies found for: Failure to Thrive | **Recruiting** | Studies received from 12/12/2011 to 12/12/2016
https://clinicaltrials.gov/ct2/results?term=Failure+to+Thrive&type=&rslt=&recr=Recruiting&age_v=&gndr=&cond=&intr=&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=12%2F12%2F2011&rcv_e=12%2F12%2F2016&lup_s=&lup_e=

5 studies found for: Failure to Thrive | **Active, not recruiting** | Studies received from 12/12/2011 to 12/12/2016
https://clinicaltrials.gov/ct2/results?term=Failure+to+Thrive&type=&rslt=&recr=Active%2C+not+recruiting&age_v=&gndr=&cond=&intr=&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=12%2F12%2F2011&rcv_e=12%2F12%2F2016&lup_s=&lup_e=

24 studies found for: Failure to Thrive | **Completed** | Studies received from 12/12/2011 to 12/12/2016
https://clinicaltrials.gov/ct2/results?term=Failure+to+Thrive&type=&rslt=&recr=Completed&age_v=&gndr=&cond=&intr=&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=12%2F12%2F2011&rcv_e=12%2F12%2F2016&lup_s=&lup_e=